Orginal Article

Genetic Expression of Transient Receptor Potential Channels in Plaque Psoriasis

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Abstract

Aim: Psoriasis is an immune-associated cutaneous condition characterized by inflammation. The transient receptor potential canonical (TRPC), transient receptor potential ankyrin (TRPA), transient receptor potential melastatin (TRPM), transient receptor potential vanilloid (TRPV), transient receptor potential polycystin (TRPP), and transient receptor potential mucolipin (TRPML) families are mammalian transient receptor potential (TRP) channels, and abnormal differentiation or barrier dysfunction may be attributed to their abnormal expression. This study aimed to investigate gene expression in TRP channels in psoriatic cases and to associate the expression level with disease severity.

Methods: This research was case-controlled and comprised 60 patients with psoriasis vulgaris and 60 years and sex-coordinated well-health volunteers as the control group. The patient's entire history was recorded, and a general and complete dermatological examination was performed. The disease severity was evaluated by applying the psoriasis area and severity index score. Venous blood samples were taken for the detection of *TRPC6*, *TRPM2*, and *TRPV1* gene expression by real-time polymerase chain reaction.

Results: Considering TRPC6; the mean expression level was lower in patients than in controls, with a statistically significant difference ($U = 661.5$ and $P < 0.001$). Nevertheless, TRPM2 and TRPV1 demonstrated higher expression levels in cases than controls ($U = 36$ and 78, resp., and $P < 0.001$ for both). Therefore, TRPM2 and TRPV1 can be used to distinguish cases from controls with significant accuracy ($P < 0.001$ for both).

Conclusion: Variations in TRP channel expression patterns may be involved in the etiopathogenesis of psoriasis and may be useful and promising agents for psoriasis treatment.

Keywords: Psoriasis, transient receptor potential channels, polymerase chain reaction

Introduction

Psoriasis is a persistent, inflammatory cutaneous illness affecting up to 3% of the global population. The prevalence of this condition varies by location and has a substantial impact on quality of life for affected individuals.[1] Psoriasis can be classified into five primary types: erythrodermic, pustular, inverted, guttate (eruptive), and plaque. Approximately 90% of cases are categorized as plaque psoriasis, which is characterized by symmetrically distributed, raised, and sharply defined scaly plaques on the scalp, knees, elbows, and lower back.[2]

Psoriasis is a complex illness caused by genetic, environmental, psychogenic, and metabolic factors. Excessive alcohol use and smoking can aggravate psoriasis, whereas the key mechanisms contributing to the development of psoriasis are related to the interactions between keratinocytes and immune system cells, such as dendritic cells, T-lymphocytes, neutrophils, and mast cells.[3]

Submission: 13-Oct-2024 **Web Publication:** 30-Dec-2024
Acceptance: 20-Nov-2024

Access this article online
Quick Response Code:
Website: www.turkjdermatol.com
DOI: 10.4274/tjd.galenos.2024.79188

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How to cite this article: Shehata WA, Hammam M, Fatma Mohamed Ghoneim FM, Azmy R. Genetic expression of transient receptor potential channels in plaque psoriasis. Turk J Dermatol. 2024;18(4):139-156.

The transient receptor potential (TRP) channels assist receptor cells in controlling the sense of environmental alterations, such as temperature, pH variations, itching perception, and pain perception. Furthermore, they are crucial for molecular signal transduction cascades involved in several skin purposes, such as epidermal proliferation and differentiation of the epidermis and programed death.[4] Indeed, they are linked to the occurrence of various cutaneous disorders, such as psoriasis, atopic dermatitis, psoriasis, rosacea, and skin tumors.[5]

Six subfamilies, including transient receptor potential vanilloid (TRPV), transient receptor potential canonical (TRPC), transient receptor potential ankyrin (TRPA), transient receptor potential polycystin (TRPP), transient receptor potential melastatin (TRPM), and transient receptor potential mucolipin (TRPML) compromise the TRP channels based on amino acid sequence homology. In human keratinocytes, members of the TRPC, TRPV, TRPM, and TRPA subfamilies were discovered.[6] Cells in the epidermis, specifically keratinocytes, express various calcium channels, most of which are non-selective ion channels belonging to the TRP channel superfamily.[7]

The skin's protective epithelial barrier is constantly regulated, with a crucial balance between keratinocyte differentiation and proliferation. The diminished keratinocyte differentiation and proliferation can lead to significant skin conditions, such as atopic dermatitis and psoriasis. This process involves various TRP channels that are essential for the influx of Ca^{2+}.[8]

This study examined the genetic expression of TRPC6, TRPM2, and TRPV1 in plaque psoriasis using real-time polymerase chain reaction (RT-PCR) and associated their expression levels with available clinical information.

Materials and Methods

This case-control study involved 120 individuals categorized into two sets. The first set included 60 cases diagnosed and appraised clinically as chronic plaque psoriasis, and the second set included 60 sex- and age-matched controls. From July 2022 to July 2023, cases were selected from the outpatient dermatology, andrology, and STD clinics of Menoufia University Hospital, and the diagnosis was based on comprehensive history taking and the presence of representative dusky red erythematous scaly plaques.[3]

Ethical Authorization and Contribution Agreement

Before the study began and after a brief explanation of the study's aims, informed consent was obtained from each contributor. The consent form was developed in accordance with the Declaration of Helsinki and the Quality and Improvement System requirements of the Egyptian Ministry of Health and Population. The Local Ethical Scientific Committee of the Menoufia University Faculty of Medicine, approved this study (approval number and date: 3/2022 DERMA49).

The inclusion criteria were as follows: Individuals with psoriasis vulgaris, irrespective of sex and age, who did not receive any medication for their psoriasis, either systemic for six weeks or topical treatment, except emollients for 15 days prior to sample collection.

The exclusion criteria were as follows: Any patient with an inflammatory or autoimmune disorder; patients with other types of psoriasis except plaque psoriasis.

A comprehensive history was obtained, including patient name, age, sex, onset of psoriasis (either late onset after age 40 or early onset before age 40), and disease duration in years. Additionally, medical history was evaluated, focusing on disease course (either progressive or stationary) and family history of psoriasis. Then, a detailed dermatological examination was conducted to identify the site of affection, scalp affection, nail affection, and presence of koebnerization.

For each patient, disease severity was evaluated by applying the psoriasis area severity index (PASI) score, which was based on a complicated computation involving the percentage of the body surface affected by psoriasis, intensity of redness, flaking, and psoriatic patch thickness. The body was divided into four structural portions: cranium, trunk, and upper and lower limbs. Separate calculations were made for the lesion's severity and the extent of the covered body surface. On a scale of 0-4, erythema, infiltration, and desquamation were measured, and on a scale of 0-6, the involved body surface area was calculated.[3] Mild was defined when PASI is < 7, moderate when PASI is 7-12, and severe disease when the PASI score is > 12.[9]

Blood Sampling

Every subject underwent a sterile venipuncture performed in a completely sterile setting using disposable syringes, with minimum venous stasis and no foaming. Then, 3 mL of venous blood was withdrawn and placed into a vacutainer tube containing ethylenediaminetetraacetic acid (EDTA), which was used for total RNA extraction and further PCR.

TRPC6, *TRPM2*, and *TRPV1* Gene Expression by RT-PCR

QIAamp RNA Blood MiniKit (Qiagen, USA) was used for high-quality total RNA extraction, followed by RNA quality and purity measurement using a Nanophotometer N60 (IMPLEN GMBH, Germany). At 260 and 280 nm; the absorbance of the RNA sample was measured.

Two-step RT-PCR was performed as follows. First step: Complementary DNA (cDNA) was synthesized from RNA extract as 4 µL of 5x TransAmp buffer, 1 µL of reverse transcriptase enzyme, and 5 µL of RNase-free water were combined with RNA extract of 10 µL using highly reproducible first-strand cDNA synthesis MyTaq One-Step RT-PCR Kit (Bioline Meridian Bioscience, London, UK). The reverse transcriptase enzyme was stopped by a single cycle of 10 min at 25 °C, 15 min at 42 °C, and 5 min at 85 °C using an Applied Biosystems 2720 thermal cycler (Bioline, Singapore, USA). At -20 °C, the resultant cDNA was stored.

Second Step: Using the SensiFAST™ SYBR® Lo-ROX Kit (Bioline Meridian Bioscience, London, UK) and a premade QuantiTect Primer Assay (Qiagen, USA), SYBR green-based quantitative RT-PCR was performed using cDNA. To assess the amount of gene expression, the following primers (Midland, Texas) were used: primers for TRPC6 F (5′-ATTCTGAATGGGGATGTTGAA-3′) and R (5′-GCAAGTTTTAAACGGCTGAGA-3′); primers for TRPM2 F (5′-CAGCCTCTTCAAGAGCTGGA-3′) and R (5′-CCACACTGACACACCACCTT-3′); primers for TRPV1 F (5′-CATGCTCAACCTGCACGA-3′) and R (5′-GCTGTCTGGCCCTTGTAGTA-3′); primers for beta-actin_F (5′- ATTGGCAATGAGCGGTTC-3′) and R (5′-CGTGGATGCCACAGGAC-3′) as endogenous control.[10]

Moreover, 5 µL of the cDNA was added to 10 µL of 2x SYBR® Low-ROX MasterMix, 1 µL of each primer, and 4 µL of RNase-free water to create a mixture of 20 µL. In 45 cycles; the reaction was carried out, with 30 s spent for denaturation at 94 °C, 30 s spent for annealing at 55 °C, and 30 s spent for extension at 72 °C. Analysis of data was done by the Applied Biosystems 7500 software (version 2.0.1). Relative quantification was used to measure mRNA levels. Furthermore, the ΔΔCt method was employed to standardize the quantity of the target gene against β-actin; an endogenous reference gene, for comparison with the control. Melting analysis was conducted to verify the absence of primer dimers.[11]

Statistical analysis

Using Epi Info 2000 and SPSS version 20 on an IBM personal computer; statistical analysis was performed. (A) Validated quantitative data were specified as mean ($\bar{X}$), standard deviation (SD), and range. Descriptive statistics were expressed as numerical amounts (N) and percentages (%); also, (B) analytical statistics were used. An investigation into the relationship between two qualitative variables was conducted using the chi-square test (χ^2). Mann-Whitney U test, also known as the non-parametric test, is a significance test used to compare two groups with quantitative variables that are not regularly distributed. A non-parametric test of significance, the Kruskal-Wallis test, compares three or more groups with quantitative variables that are not regularly distributed. Spearman's correlation (r) test was used to quantify the association between quantitative and qualitative ordinal data. In receiver operating characteristic curves, the cut-off value with the highest accuracy was designated as the diagnostic cutoff point. $P < 0.05$ was the level of significance.[12]

Results

There were 29 (48.3%) women and 31 (51.7%) men. Their age extended from 26 to 68 years, with 45.0±11.72 years presented as $\bar{X}$ ± SD value. The control group included 29 (48.3%) females and 31 (51.7%) males. Their age extended from 26 to 68 years with 43.78±11.98 years old as $\bar{X}$ ± SD value, without noteworthy differences in gender and age ($P > 0.05$ for both). The clinical characteristics of the studied cases are presented in Table 1.

Evaluation of the Mean Expression Levels of TRPC6, TRPM2, and TRPV1 Between the Study and Control Groups

The mean expression level of TRPC6 was statistically significant, being lower in cases than in controls ($U = 661.5$ and $P < 0.001$). Furthermore, regarding TRPM2 and TRPV1; the mean expression levels were higher in cases than in controls, with statistically significant differences between cases and controls ($U = 36$ and 78, resp., and $P < 0.001$ for both), as depicted in Table 2.

Table 1. Clinical information of the studied patients (n = 60)

	n (%)
Onset	
Early	27 (45.0)
Late	33 (55.0)
Course	
Stationary	21 (35.0)
progressive	39 (65.0)
Duration of the disease (years)	
Min.-max.	1.0-8.0
Mean ± SD	3.75±2.07
Median (IQR)	3.0 (2.0-5.0)
Family history	
Positive	29 (48.3)
Negative	31 (51.7)
Risk factors	
Yes	18 (30.0)
DM	2 (13.3)
HTN	9 (15.0)
HTN, DM	1 (15.0)
Smoking	6 (10.0)
No	42 (70.0)

Table 1. Continued

	n (%)
Site of affection	
Extremities	16 (26.7)
Axial, extremities	33 (55.0)
Axial	11 (18.3)
Scalp involvement	
Yes	37 (61.7)
No	23 (38.3)
Nail involvement	
Yes	26 (43.3)
No	34 (56.7)
Joint involvement	
Yes	19 (31.7)
No	41 (68.3)
Palm & sole involvement	
Yes	22 (36.7)
No	38 (63.3)
Itching	
Yes	39 (65.0)
No	21 (35.0)
Koebnerization	
Yes	28 (46.7)
No	32 (53.3)
PASI score	
Min.-max.	1.20-30.40
Mean ± SD	11.53±7.60
Median (IQR)	9.45 (5.45-16.05)
Severity	
Mild	20 (33.3)
Moderate	20 (33.3)
Severe	20 (33.3)

Min.: Minimum, Max.: Maximum, SD: Standard deviation, IQR: Interquartile range, DM: Diabetes mellitus, HTN: Hypertension, PASI: Psoriasis area severity index

Association Between Mean TRPC6 Expression and Clinical Information of Patients

The mean expression TRPC6 level was significantly associated with the site of affection (H = 13,137, P = 0.001), scalp affection (U = 268.5, P = 0.017), joint affection (U = 172.5, P = 0.001), itching (U = 169.5, P < 0.001), koebnerization (U = 310.5, P = 0.042), and severity, which was higher in mild cases (U = 34,862, P < 0.001), as shown in Table 3. Furthermore, significant negative correlations between TRPC6 and disease duration in years (r = -0.410, P = 0.001) and PASI score (r = -0.736, P < 0.001) were documented (Figure 1a).

Association Between Mean TRPM2 Expression and Clinical Records of Patients

Higher mean TRPM2 expression was significantly associated with the course of psoriasis (U = 260,000, P = 0.021), scalp involvement (U = 195,000, P < 0.001), nail involvement (U = 244,000, P = 0.003), joint involvement (U = 266,000, P = 0.049), itching (U = 236,000, P = 0.007), koebnerization (U = 256.000, P = 0.004), and severity, which was higher in severe cases (U = 27,620, P < 0.001), as demonstrated in Table 4. Moreover, significant positive correlations were observed between the mean TRPM2 expression level and disease duration in years (r = 0.339, P = 0.008) and PASI score (r = 0.561, P < 0.001) were revealed (Figure 1b).

Association Between Mean TRPV1 Expression and Clinical Information of Patients

The higher mean expression level of TRPV1 was significantly associated with the course of disease (U = 272,000, P = 0.033), scalp involvement (U = 294,000, P < 0.046), nail involvement (U = 282,000, P = 0.017), joint involvement (U = 256,000, P = 0.034), palm and sole involvement (U = 289,000, P = 0.048),

Table 2. Comparison concerning mean expression level of TRPC6, TRPM2, TRPV1 between patients and control subjects

	Patients, (n = 60)	Control subjects, (n = 60)	Test of significance	P
TRPC6			**U**	
Min.-max.	0.19-2.95	1.0-3.78	661,500	<0.001*
Mean ± SD	1.10±0.66	1.92±0.67		
Median (IQR)	0.96 (0.59-1.57)	1.79 (1.48-2.25)		
TRPM2			**U**	
Min.-max.	1.48-9.87	0.54-1.95	36,000	<0.001*
Mean ± SD	4.87±2.41	1.23±0.34		
Median (IQR)	4.55 (2.77-6.32)	1.10 (1.0-1.47)		
TRPV1			**U**	
Min.-max.	1.06-9.87	0.10-1.87	78,000	<0.001*
Mean ± SD	4.75±2.67	0.97±0.36		
Median (IQR)	4.11 (2.64-6.90)	1.0 (0.79-1.09)		

Min.: Minimum, Max.: Maximum, SD: Standard deviation, IQR: Interquartile range, U: Mann-Whitney U test, TRPC6: Transient receptor potential canonical 6, TRPM2: Transient receptor potential melastatin 2, TRPV1: Transient receptor potential vanilloid 1, P: For comparing between the two studied groups, $P \leq 0.05$ is the level of significance, *: Significant

Table 3. Association concerning mean expression level of TRPC6 and clinical information of the studied patients

		TRPC6			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Sex					
Male	31	0.95±0.49	0.94 (0.19-2.09)	U=358,000	0.176
Female	29	1.26±0.79	0.99 (0.21-2.95)		
Onset					
Early	27	0.98±0.63	0.70 (0.19-2.32)	U=347,000	0.143
Late	33	1.20±0.68	0.99 (0.19-2.95)		
Course					
Stationary	21	1.27±0.85	0.95 (0.21-2.95)	U=358,000	0.425
Progressive	39	1.01±0.52	0.98 (0.19-2.42)		
Family history					
Positive	29	1.14±0.70	0.99 (0.19-2.95)	U=423,500	0.700
Negative	31	1.07±0.64	0.88 (0.19-2.42)		
Risk factors					
DM	1		1.35	H=3,295	0.348
HTN	9	1.51±0.95	1.10 (0.32-2.95)		
HTN, DM	2	1.32±0.47	1.32 (0.99-1.66)		
Smoking	6	1.04±0.59	1.11 (0.19-1.72)		
No	42	1.01±0.60	0.86 (0.19-2.32)		
Site of affection					
Extremities	16	1.63±0.69	1.65 (0.68-2.95)	H=13,137*	0.001*
Axial, extremities	33	0.88±0.48	0.71 (0.19-2.12)		
Axial	11	1.01±0.71	0.94 (0.21-2.32)		
Scalp involvement					
Yes	37	0.97±0.65	0.71 (0.19-2.95)	U=268,500*	0.017*
No	23	1.32±0.63	1.10 (0.32-2.42)		
Nail involvement					
Yes	26	0.95±0.64	0.80 (0.19-2.95)	U=321,500	0.072
No	34	1.22±0.66	1.26 (0.21-2.42)		
Joint involvement					
Yes	19	0.67±0.38	0.63 (0.19-1.56)	U=172,500*	0.001*
No	41	1.30±0.67	1.28 (0.19-2.95)		
Palm & sole involvement					
Yes	22	1.05±0.75	0.94 (0.19-2.95)	U=365,500	0.421
No	38	1.13±0.61	1.04 (0.21-2.42)		
Itching					
Yes	39	0.86±0.49	0.76 (0.19-2.12)	U=169,500*	<0.001*
No	21	1.56±0.71	1.57 (0.59-2.95)		
Koebnerization					
Yes	28	0.94±0.66	0.80 (0.19-2.95)	U=310,500*	0.042*
No	32	1.25±0.64	1.17 (0.28-2.42)		
Severity					
Mild	20	1.69±0.67	1.75 (0.59-2.95)	H=34,862*	<0.001*
Moderate	20	1.11±0.33	1.01 (0.32-1.57)		
Severe	20	0.50±0.22	0.54 (0.19-0.99)		

TRPC6: Transient receptor potential canonical 6, SD: Standard deviation, Min.: Minimum, Max.: Maximum, IQR: Interquartile range, $P \leq 0.05$ is the level of significance, DM: Diabetes mellitus, HTN: Hypertension, *: Significant, U: Mann-Whitney U test, H: H for Kruskal-Wallis test, *P*: For comparing between different categories

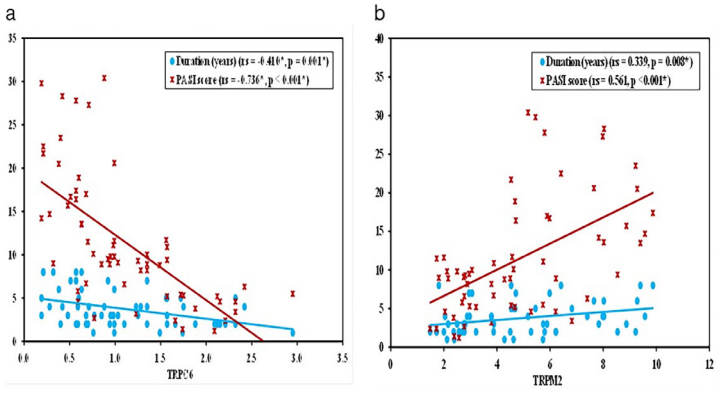

Figure 1. (a) Correlation between TRPC6 and disease duration in years and PASI score, (b) correlation between mean TRPM2 level and disease duration in years and PASI score
TRPC6: Transient receptor potential canonical 6, TRPM2: Transient receptor potential melastatin 2, PASI: Psoriasis area severity index

Table 4. Association concerning mean expression level of TRPM2 and clinical information of the studied patients (n = 60)

		TRPM2			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Sex					
Male	31	5.22±2.60	4.62 (1.48-9.87)	U=386,000	0.348
Female	29	4.51±2.18	4.53 (1.72-9.57)		
Onset					
Early	27	5.31±2.65	4.71 (1.72-9.87)	U=368,000	0.249
Late	33	4.52±2.17	4.28 (1.48-9.22)		
Course					
Stationary	21	4.02±2.46	2.77 (1.48-9.57)	U=260,000*	0.021*
Progressive	39	5.34±2.28	4.68 (1.73-9.87)		
Family history					
Positive	29	5.22±2.38	4.57 (2.12-9.87)	U=371,000	0.246
Negative	31	4.55±2.43	3.88 (1.48-9.57)		
Risk factors					
DM	1#		2.88	H=0.319	0.956
HTN	9	4.67±1.99	4.68 (1.81-7.40)		
HTN, DM	2	4.57±4.37	4.57 (1.48-7.65)		
Smoking	6	4.45±1.19	4.60 (2.50-5.79)		
No	42	5.04±2.61	4.55 (1.72-9.87)		
Site of affection					
Extremities	16	4.09±1.77	4.20 (1.72-7.40)	H=3,497	0.174
Axial, extremities	33	5.42±2.64	5.17 (1.48-9.87)		
Axial	11	4.37±2.25	3.79 (2.04-9.28)		
Scalp involvement					
Yes	37	5.68±2.39	5.45 (1.73-9.87)	U=195,000*	<0.001*
No	23	3.58±1.84	2.77 (1.48-7.65)		
Nail involvement					
Yes	26	5.91±2.36	5.77 (2.00-9.87)	U=244,000*	0.003*
No	34	4.08±2.16	3.50 (1.48-9.57)		
Joint involvement					
Yes	19	5.90±2.78	5.45 (2.00-9.87)	U=266,000*	0.049*
No	41	4.40±2.09	3.88 (1.48-8.87)		

Table 4. Continued

		TRPM2			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Palm & sole involvement					
Yes	22	5.71±2.66	5.59 (2.00-9.87)	U=306,000	0.086
No	38	4.39±2.14	3.88 (1.48-9.28)		
Itching					
Yes	39	5.47±2.54	5.17 (1.48-9.87)	U=236,000*	0.007*
No	21	3.77±1.72	2.77 (1.72-7.40)		
Koebnerization					
Yes	28	5.79±2.31	5.59 (2.00-9.87)	U=256,000*	0.004*
No	32	4.08±2.24	3.14 (1.48-9.57)		
Severity					
Mild	20	3.76±1.74	3.09 (1.48 -7.40)	H=27,620	<0.001*
Moderate	20	3.64±1.73	3.01 (1.73-8.54)		
Severe	20	7.22±1.84	7.74 (4.53-9.87)		

TRPM2: Transient receptor potential melastatin 2, Min.: Minimum, Max.: Maximum, SD: Standard deviation, DM: Diabetes mellitus, HTN: Hypertension, U: Mann-Whitney U test, $P \leq 0.05$ is the level of significance, *: Significant, H: H for Kruskal-Wallis test, *P*: For comparing between different categories

koebnerization ($U = 300{,}000$, $P = 0.028$), and severity, which was higher in severe cases ($U = 19{,}279$, $P < 0.001$) (Table 5). Furthermore, a significant positive correlation was detected between the mean TRPV1 level and the PASI score ($r = 0.469$, $P < 0.001$) (Figure 2a).

Receiver Operating Characteristic Curves for TRPC6, TRPM2, and TRPV1 in Healthy Subjects

With a sensitivity of 80.0, specificity of 63.33, and cutoff value of ≤ 1.66, TRPC6 can distinguish cases from controls with significant accuracy. With sensitivity and specificity of 95.0 and > 1,731 at the cutoff value, TRPM2 can be used to identify cases from controls with considerable accuracy. With a cutoff value of > 1.389, sensitivity of 93.33, and specificity of 88.33, TRPV1 can effectively differentiate cases from controls with significant accuracy ($P < 0.001$; for all) (Figure 2b).

Discussion

Psoriasis is a multifactorial inflammatory disease with a chronic course and multifaceted etiopathogenesis.[13] Recently, Kim et al.[14] revealed that keratinocytes, immune cells, dendritic cells, and the peripheral nervous system are affected by ion channels. The delicate balance between keratinocyte proliferation and differentiation governs the continuous control of the skin's protective epithelial barrier.[15]

The current study showed that the expression of TRPC6 was lower in cases than in controls, and their expression levels were negatively correlated with the PASI score. This was in agreement with Özcan et al.,[5] who detected that the mRNA expression level of TRPC6 was decreased in cases than in control subjects ($P = 0.009$) and stated that the keratinocyte maturation degree is dependent upon the calcium gradient within the cell. Also, they documented that the downregulation of TRPC6 channels is associated with a decrease in keratinocyte differentiation, signifying the potential utility of TRPC activators in psoriasis treatment.

In normal healthy skin, the levels of extracellular Ca^{2+} ($[Ca^{2+}]$) significantly increase as the epidermis moves from the basal to the spinous layer. Dysfunctions in the calcium gradient, which is believed to play a crucial role in controlling keratinocyte maturation, could account for changes in the growth and development of psoriatic keratinocytes. TRPC6 proteins play a significant role in regulating differentiation triggered by high $[Ca^{2+}]_{ex}$.[16]

Leuner et al.[17] reported that upon exposure of psoriatic keratinocytes to high extracellular Ca^{2+}, a slight influx of Ca^{2+} was detected because the surface membrane of these keratinocytes exhibited weakened functional expression of the TRPCs and downregulation of TRPC6 channels, which were associated with impaired keratinocyte differentiation. In contrast, in normal keratinocytes, the exact circumstances; at the start of the cell differentiation program and a corresponding increase in intracellular Ca^{2+}.

The current study revealed that TRPM2 level in cases of psoriasis was significantly higher than normal healthy controls. This was similar to the research by Özcan et al.,[5] who established that the mRNA expression level of TRPM2 was higher in cases than in control subjects ($P = 0.001$) and stated that TRPM2 is a sensor for reactive oxygen species (ROS) that aggravates psoriasis pathogenesis and that TRPM2 expression plays a key part in the proliferation of T-cells

Table 5. Association concerning mean expression level of TRPV1 and clinical information of the studied patients (n = 60)

		TRPV1			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Sex					
Male	31	5.16±2.74	5.12 (1.06-9.87)	U=373,000	0.258
Female	29	4.31±2.57	3.59 (1.37-9.39)		
Onset					
Early	27	4.60±2.49	4.55 (1.06-8.96)	U=423,000	0.738
Late	33	4.88±2.85	3.88 (1.35-9.87)		
Course					
Stationary	21	3.75±2.53	2.98 (1.35-9.21)	U=272,000*	0.033*
Progressive	39	5.29±2.62	4.77 (1.06-9.87)		
Family history					
Positive	29	5.01±2.61	4.55 (1.06-9.87)	U=398,000	0.446
Negative	31	4.51±2.75	3.82 (1.35-9.39)		
Risk factors					
DM	1		3.55	H=1,959	0.581
HTN	9	4.96±3.07	4.29 (1.37-9.21)		
HTN, DM	2	5.28±4.95	5.28 (1.78-8.78)		
Smoking	6	6.00±2.23	5.67 (3.46-9.87)		
No	42	4.53±2.62	3.85 (1.06-9.39)		
Site of affection					
Extremities	16	4.35±2.65	3.46 (1.57-9.21)	H=3,473	0.176
Axial, extremities	33	5.32±2.75	5.12 (1.35-9.87)		
Axial	11	3.63±2.17	3.48 (1.06-7.56)		
Scalp involvement					
Yes	37	5.30±2.64	4.78 (1.06-9.87)	U=294,000*	0.046*
No	23	3.86±2.53	3.26 (1.37-8.92)		
Nail involvement					
Yes	26	5.71±2.76	5.73 (1.35-9.87)	U=282,000*	0.017*
No	34	4.01±2.39	3.51 (1.06-8.96)		
Joint involvement					
Yes	19	5.90±2.80	6.73 (1.35-9.87)	U=256,000*	0.034*
No	41	4.22±2.47	3.82 (1.06-9.21)		
Palm & sole involvement					
Yes	22	5.64±2.70	5.25 (1.39-9.87)	U=289,000*	0.048*
No	38	4.24±2.55	3.57 (1.06-9.39)		
Itching					
Yes	39	5.20±2.68	4.78 (1.06-9.87)	U=296,000	0.079
No	21	3.92±2.52	3.46 (1.39-9.21)		
Koebnerization					
Yes	28	5.57±2.56	5.50 (1.35-9.87)	U=300,000*	0.028*
No	32	4.03±2.59	3.68 (1.06-8.96)		
Severity					
Mild	20	3.73±2.65	3.04 (1.06-9.21)	H=19,279*	<0.001*
Moderate	20	3.60±1.74	3.57 (1.35-7.56)		
Severe	20	6.92±2.16	7.03 (2.98-9.87)		

TRPV1: Transient receptor potential vanilloid 1, Min.: Minimum, Max.: Maximum, SD: Standard deviation, U: Mann-Whitney U test, H: H for Kruskal-Wallis test, *P*: For comparing between different categories, *: Statistically significant at $P \leq 0.05$

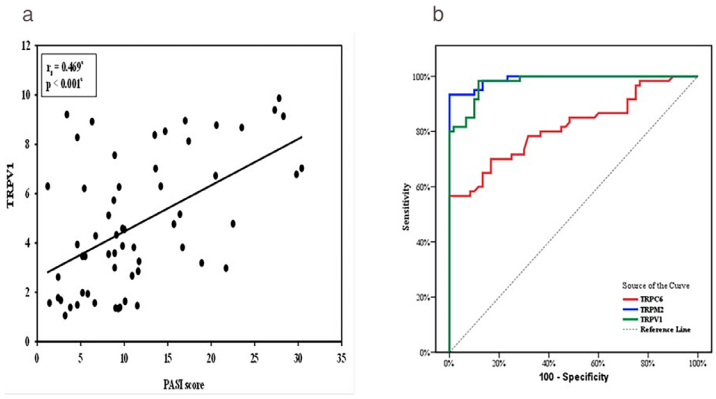

Figure 2. (a) Correlation between mean TRPV1 level and PASI score, (b) Receiver operating characteristic curve for TRPC6, TRPM2, and TRPV1 to discriminate cases from controls.
TRPV1: Transient receptor potential vanilloid 1, TRPC6: Transient receptor potential canonical 6, TRPM2: Transient receptor potential melastatin 2, PASI: Psoriasis area severity index

and proinflammatory cytokine production following T-cell receptor (TCR) stimulation.

TRPM2 is a non-selective, permeable Ca^{2+} cation channel that is conveyed in several types of innate immunity cells, such as dendritic cells, monocytes/macrophages, and adaptive immunity cells, such as T- and B-cells.[18]

Following TCR activation, TRPM2 channel expression is upregulated in T-cells. TRPM2 channels may be activated by TCR stimulation, which releases cyclic adenosine diphosphate ribose from the endoplasmic reticulum. This occurs notwithstanding the absence of direct evidence linking TRPM2 channels to Ca^{2+} influx in lymphocytes or T-cell activity. Additionally, NAD^{+} precursors control Ca^{2+} homeostasis through ADPR-mediated gating of TRPM2 channels, which, in response to mitogens; TRPM2 channels upregulate essential T-cell processes such as proliferation and interleukin-2 (IL-2) production.[19]

Melzer et al.[20] revealed that TRPM2 expression is present in primary CD^{4+} T-cells, and this expression aids in T-cell proliferation and proinflammatory cytokine generation upon TCR stimulation.

Significant positive correlations between the mean expression level of TRPM2 and PASI were found in the current study. Numerous studies have demonstrated that elevated reactive nitrogen species and ROS exacerbate psoriasis. TRPM2 acts as a sensor for ROS; thus, inflammatory cytokines are secreted as a result of the antioxidant defense system that is built up against this illness, and this is what causes skin inflammation.[21,22]

The current study displayed that the TRPV1 level in patients with psoriasis was higher than that of controls, with significant results. This was in the same line with Özcan et al.,[5] who established that the expression level of TRPV1 mRNA expression was elevated in the studied cases compared with controls (P = 0.028) and stated that primary human T-cells express TRPV1, resulting in Ca^{2+} influx and TCR-mediated T-cell activation. TRPV1 blockers also prevent T-cell activation and inflammatory cytokine release.

Yun et al.[23] found that the symptoms of a disease akin to atopic dermatitis, as indicated by a reduced transepidermal water loss score, can be inhibited by pharmacologic blocking of TRPV1 activation. Restoring the neutral lipid layer and reversing alterations in the production of loricrin and filaggrin-two essential epidermal barrier proteins that are decreased in psoriasis-are prerequisites for this inhibition.

Kashem et al.[24] reported that the synthesis of IL-23 by $CD301b^{+}$ dendritic cells is crucial for the production of IL-17 from T-17 cells. Skin innervation and IL-23 production are strategically connected, with calcitonin gene-related peptide (CGRP), produced by $TRPV1^{+}$ neurons, acting as the main stimulant for dendritic cells to synthesize IL-23.

On the other hand, the etiopathogenesis of psoriasis is referred to as IL-23.[25] In IL-23-dependent imiquimod (IMQ)-induced psoriasis-like skin inflammation, $TRPV1^{+}$ nociceptive sensory neurons are interrelated with dendritic cells to produce IL-23, thus controlling IL-17 and 22 production by $IL23R^{+}$ dermal γδ T-cells, which determine cutaneous inflammation skin.[26]

Additionally, Zhou et al.[27] documented a significant decrease in hyperplasia of the epidermis, dermal inflammatory cellular infiltrate, and production of cytokines such as IL-1, IL-6, and IL-23 in TRPV1-knockout mice treated with IMQ.

The current study showed that the relationship between mean TRPV1 expression and itching was non-significant. On the contrary, other studies reported a significant relationship between itching and TRPV1 level.[28,29] This difference may be attributed to different sample sizes, different ethnic

backgrounds of the studied population, and diverse clinical situations of the studied cases in each research.

Zhu et al.[30] reported a substantial association between innervation and psoriasis, suggesting that neurocutaneous pathways affect psoriasis development. Psoriatic plaques were cleared in the affected dermatomal regions with denervation due to either myelitis or traumatic damage. In contrast, the return of psoriasis lesions in the affected area was associated with the recovery of neural function following nerve loss. The discovery of significantly elevated TPRV1 signals in the psoriasis plaque epidermis further points to neurogenic component involvement in the psoriasis growth process. Moreover, psoriasis lesions express more of the neuropeptide CGRP, which is related to TRPV1.[31]

Future research should be more extensive, focusing on the investigation of TRP channels in various forms of psoriasis and encompassing diverse patient groups, including those with mild and severe cases.

Study limitations

The limitations of this study were the limited sample size, as cases were collected from one center, together with the limited availability of diagnostic instruments.

Conclusion

Diverse patterns of TRP channel expression in patients with chronic plaque psoriasis may play a role in psoriasis pathogenesis. These channels are therefore essential pharmacological targets for novel psoriasis treatments and serve as candidate targets for psoriatic skin disease treatment.

Ethics

Ethics Committee Approval: The Local Ethical Scientific Committee of the Menoufia University Faculty of Medicine, approved this study (approval number and date: 3/2022 DERMA49).

Informed Consent: Informed consent was obtained from each contributor.

Footnotes

Authorship Contributions

Concept: W.A.S., M.H., F.M.G., Design: W.A.S., M.H., F.M.G., Data Collection or Processing: W.A.S., R.A., Analysis or Interpretation: W.A.S., F.M.G., R.A., Literature Search: W.A.S., F.M.G., R.A., Writing: W.A.S., M.H., F.M.G., R.A.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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